National Toxicology Program Executive Committee Meeting
July 27, 2017
1:00-4:00 pm

Hubert Humphrey Building
Room 425A, 200 Independence Avenue, SW
Washington, DC 20201

Summary Minutes

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I. Attendees

Members in Attendance

Dr. Linda Birnbaum, National Institute of Environmental Health Sciences/National Toxicology Program (NIEHS/NTP) (Chair)
Dr. Patrick Breyesse, National Center for Environmental Health/Agency for Toxic Substances and Disease Registry (NCEH/ATSDR)
Dr. John Bucher, NIEHS/NTP
Dr. Robert Kavlock, Environmental Protection Agency (EPA)
Dr. Elaine Knight, National Cancer Institute (NCI) [alternate for Dr. Toby Hecht] [via WebEx]
Mr. Gib Mullan, Consumer Product Safety Commission (CPSC) [alternate for Acting Chairman Ann Marie Buerkle]
Dr. Palmer Orlandi, Food and Drug Administration (FDA) [alternate for CAPT. Denise Hinton]
Dr. William Perry, Occupational Safety and Health Administration (OSHA)
Dr. Patricia Underwood, Department of Defense (DoD)
Dr. Elizabeth Whelan, National Institute for Occupational Safety and Health (NIOSH) [alternate for Dr. John Howard]

Points of Contact (POC)

Dr. Karen Hamernik, EPA
Dr. Kristina Hatlelid, CPSC
Dr. Goncarlo Gamboa da Costa, FDA

Agency Staff

Dr. Chad Blystone [via WebEx]
Dr. Warren Casey, NIEHS
Dr. Michael DeVito, NIEHS
Dr. Suzanne Fenton, NIEHS [via WebEx]
Dr. Suzanne Fitzpatrick, FDA
Dr. Lynn Flowers, EPA
Dr. Sandra Howard, Office of the Assistant Secretary for Health, HHS
Dr. Aubrey Miller, NIEHS
Ms. Anna Lee Mosley, NIEHS
Dr. Kathleen Raffaele, EPA [via WebEx]
Dr. Louis Scarano, EPA
Dr. Stephanie Smith-Roe, NIEHS [via WebEx]
Dr. Christopher Weis, NIEHS

II. Welcome and Introductions

Dr. Birnbaum, chair, called the meeting to order at 1:00 pm and welcomed everyone. Committee members, their designees, and agency staff in attendance introduced themselves.

III. ICCVAM National Strategy

Dr. Warren Casey, Director of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), updated the committee on efforts to establish a roadmap to new approaches for safety testing, spearheaded by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), which NICEATM supports. The roadmap aims to improve the human relevance of

toxicity testing and reduce the use of animals. It is directed at the 16 ICCVAM agencies, seeking to establish the U.S. as a leader in the field while working closely with international counterparts. It is designed to supplant the previous model for alternatives, which was 1:1 test replacement in a linear approach from method development to validation to regulatory acceptance to industry adoption, which has been recognized as ineffective. The new approach incorporates utilization, confidence, and technology in an interconnected, circular model, and starts with the end users, the regulatory agencies, determining their needs and working backward from there. Successful development and implementation of the new approaches will require integrated efforts that address three strategic goals:

- Encourage the adoption and use of new methods and approaches by federal agencies and regulated industries.
- Foster the use of efficient, flexible, and robust practices to establish confidence in new methods.
- Help end users guide the development of the new tools needed to support their needs.

Dr. Casey described how the new roadmap differs from prior efforts:

- It is driven by Federal agencies.
- It includes both chemicals and medical products.
- It will be paired with implementation plans that are tracked and publicly reported.

He cited several examples of projects in progress, and supplied a timeline, noting the intent to publish the final roadmap in November 2017 and multiple opportunities for public input.

Comments and questions

- In response to a question from Dr. Underwood, Dr. Casey noted that validating methods that lower attrition and are applicable to early screening would be a focus.
- Dr. Fitzgerald noted that FDA is heavily involved in examining new methods. She said the agencies are working together to help new methods become adopted via ICCVAM.
- Dr. Orlandi pointed out that it would be important to establish baselines to ensure that new methods are equivalent or superior to traditional ones.
- With regard to methods' validation, Dr. Casey observed that it would be advisable to make the validation process less stringent, particularly by eliminating the "naïve lab" requirement, and placing reduced emphasis on "one-size-fits-all" methods. The focus should be on "fit for purpose validation" and development of performance standards.
- Dr. Bucher pointed out that Congressional legislation, such as the FACT Act, would affect how ICCVAM functions. Dr. Casey noted that it would require agencies to report the type and number of toxicity tests performed. The majority of the animal welfare community has become an ICCVAM ally and hopefully can be effective in communicating with Congress about the potential negative impact of the proposed legislation. A challenge is to help Congress recognize ICCVAM's progress in approaches and technology.
- Dr. Kavlock ask whether the strategy would address the issue of the animal test as the "gold standard". Dr. Casey acknowledged this yet, unanswered challenge for validation, especially when the animal test may not be human predictive. It is a regulatory requirement to show equivalence of the alternative test to the animal test.

IV. EPA Development of a TSCA Strategy for Advancing Non-animal Testing

Dr. Louis "Gino" Scarano briefed the committee on EPA's plans to develop a strategic plan to reduce, replace, and refine vertebrate animal testing under the requirements of the amended TSCA, known as

the Frank R. Lautenberg Chemical Safety for the 21st Century Act. He summarized changes in EPA requirements related to both new and existing chemicals. New rules involving prioritization, risk evaluation, and inventory were posted June 22, 2017. The law requires that within two years of enactment (June 2016), EPA must "develop a strategic plan to promote the development and implementation of alternative test methods…and provide information of equivalent or better scientific quality and relevance for assessing risks of injury to health or the environment…" Under the law's language, the strategic plan must include scientific considerations, acceptance considerations, and other considerations such as context (e.g., new vs. existing chemicals), a list of methods and strategies, criteria for considering scientific reliability and relevance, etc.

The draft strategic plan will be created through October, 2017, with a stakeholder workshop planned for November 2017. From December 2017 to April 2018, the first draft will be completed and stakeholders consulted. The plan will be finalized April – May, 2018, and posted by June 22, 2018, in accordance with the law's requirement. Dr. Scarano listed the many organizations, both within and outside the government, with whom EPA will collaborate as the process moves forward.

Comments and questions

- Dr. Scarano noted that EPA requests the same information from all clients. The information received is considered proprietary and cannot be shared outside the agency.
- Dr. Birnbaum noted that the timeline appeared ambitious, and asked what would happen if the deadline were not met. Dr. Scarano observed that the schedule should be reasonable, and he anticipated being able to meet the deadline. He also mentioned that the law requires preparation of a progress report every five years.
- In response to a question about TSCA implementation, Dr. Scarano said that development of a strategic plan is required and it is detailed in the background materials that were provided.
- Dr. Scarano said for a new chemical, EPA must identify any concerns. He described the application process and the changes brought about by the new law. If EPA does not make a decision on an application within 90 days, the company's fee has to be returned.
- Dr. Scarano said that, unlike pesticides, industrial chemicals usually test only the primary ingredient/chemical in commerce (not all formulations).

V. Research on Per- and Polyfluoroalkylated Substances (PFAS)

A. NTP Studies: Rapid Evaluation and Assessment of Chemical Toxicity (REACT) - Per- and Polyfluoroalkyl Substances (PFAS)

Dr. Michael DeVito described the **R**apid **E**valuation and **A**ssessment of **C**hemical **T**oxicity (REACT) initiative, which is first addressing per- and polyfluoroalkyl substances (PFASs). Working with partner agencies, NTP has compiled a list of more than 40 PFOS and PFOA alternatives under study. NTP is planning to use an integrated approach that will incorporate data and information from *in silico* models, *in vitro* models, and *in vivo* models and expedite timely reporting. To facilitate screening and testing prioritization, an iterative approach will be used, with each study type informing the next, ultimately yielding prototypic chemicals from *in vitro* groupings to move on to *in vivo* studies. A component-based approach will be used to assess PFAS mixtures, as well as a whole-mixture approach to evaluate aqueous fire-fighting foam.

NTP studies include:

- Chronic bioassay
- 28-day toxicity studies
- Toxicokinetic studies
- Immunotoxicity assessment

Initial findings from PFOA *in vivo* studies show developmental effects, systemic effects, and transfer of PFOA to offspring. Dr. DeVito also noted that NTP has published a systematic review on immunotoxicity associated with exposure to PFOA or PFOS, which are "presumed to be immune hazards to humans."

Dr. Birnbaum described other PFAS studies being funded by NIEHS.

Questions and comments

- Dr. DeVito noted that a goal would be an approach that enables handoff of data to agencies to help inform their approach to the chemicals. A working group is addressing this issue. A committee member commented that a better, coordinated hand-off from the research agencies to the regulatory agencies would be welcomed.
- Dr. Weis described OSTP Toxics and Risk Subcommittee, which NIEHS has cochaired for 7 years with the EPA and Department of Defense. He noted the subcommittee's two working groups, the Exposure Science for 21st Century Working Group and the Chemical Toxicological Assessment Working Group, which is involved in coordinating all interagency aspects of science associated with public health, and therefore regulation. There are 17 agencies that regularly attend and the working group provides a good forum for communicating agency needs and sharing information.
- Dr. DeVito noted that *in vitro*-to-*in vivo* extrapolation models would be developed for all 36 PFAS, allowing estimations of equivalent human oral exposures. He said NTP currently has 22 of the 36 chemicals in pure form, with the remainder on order.

B. US EPA Cross-Agency Coordination of PFAS Activities

Dr. Robert Kavlock noted that EPA issued a health advisory related to PFAS in 2016 and since then, interest in the chemical class has "snowballed," with 9 of EPA's 10 regions identifying it as a high priority issue. PFAS coordination at EPA is led through the Office of the Science Advisor. PFAS is a multi-facted cross-agency issue, encompassing:

- Human health toxicity
- Exposure
- Analytical methods
- Risk management
- Risk communication

Currently, there are three cross-agency work groups, addressing (1) human health toxicity, (2) analytical methods, and (3) data quality issues. The working group on human health toxicity is systematically compiling information for ~30 PFASs of interest to various program offices or regions. The working group on analytical methods aims to develop multi-laboratory validated methods for 24 PFASs to analyze sample types other than drinking water. The working group on data quality is developing guidelines for data deliverable and assessment criteria.

Dr. Lynn Flowers provided additional information about the working group on human health toxicity. It aims to identify which PFASs have data and what types, how those data might be used for "read across", and how data on PFOA or PFOA might be used to inform other PFASs. The working group has started a comprehensive systematic literature review. Collectively, the information should allow EPA to develop a portfolio.

C. ATSDR PFAS Activities

Dr. Patrick Breyesse noted that publication of EPA's 2016 lifetime health advisories for PFOS and PFOA created much concern across the country. He thought that PFASs would be the environmental public health challenge of the next decade, as there is increasing evidence of their toxicity. ATSDR develops minimal risk levels (MRLs) that are used to help assess risk in communities. ATSDR has not established any MRLs for PFAS. With adoption of lower safe exposure levels for PFAS, it goes from a situation where millions of Americans are potentially at risk to tens of millions. The agency is revising the draft MRLs for PFOS and PFOA, and adding MRLs for PFNA and PFHxS. The revised draft MRLs for PFOS and PFOA are lower than EPA's health advisory levels.

Communities are asking for health risk information and biomonitoring. Health data are lacking to address community health concerns, especially for developmental and cancer effects. ATSDR has published a Exposure Assessment Toolkit to aid statistical representative sampling for biomonitoring that is being made available to states. Dr. Breyesse said three to four labs have been identified by the agency as capable of doing blood measurements in the communities given the toolkit, and there is work toward increasing that capacity. There is proposed legislative language for ATSDR to conduct a national study on PFAS at military sites, although with no accompanying appropriation.

Questions and comments

- Dr. Birnbaum noted that NIEHS through its Children's Health Exposure Analysis Resource (CHEAR) Program has funded a network of six labs for biomonitoring, where anyone with an NIH grant involving pregnant women or children can have their samples measured.
- Dr. Breyesse said ATSDR believes population-level biomonitoring is important to aid with decisions regarding interventions and does not recommend individual-level biomonitoring. In its communications, ATSDR is careful not to lead people to believe that there is any clinical diagnosis proceeding directly from biomonitoring results.
- FDA has received inquiries from states about how high PFAS levels in sources like irrigation water might translate into foods. Migration from product packaging is also a concern.
- Five states have issued PFAS advisories regarding fish consumption from contaminated waters.
- Dr. Whelan said NIOSH and OSHA are not currently conducting biomonitoring for PFAS among firefighters, but could add it to the portfolio. Committee members said that would be important for anyone living in or near an airfield.

VI. Research on Glyphosate

A. NTP Studies: Evaluation of Oxidative Stress and Genotoxicity of Glyphosate and Its Formulations

Dr. Mike DeVito reported on NTP's activities related to glyphosate, a broad-spectrum herbicide, both in its pure form and in various formulations. The specific aims of the studies are to:

- Compare the effects of glyphosate to the effects of glyphosate formulations using measures of genotoxicity, oxidative stress, and cell viability.
- Compare the dose-response relationships between oxidative stress, genotoxicity, and cell viability.
- Investigate whether there are other adverse effects of glyphosate and its formulations that require further evaluation.

NTP's work to date:

- Positive and negative controls have been evaluated in HaCaT and HepaRG cells.
- Formulations and actives have been run in HaCaT and HepaRG cells; data are being analyzed.
- Studies with TK6 cells are starting.

Results will be published as an NTP Research Report and posted to the NTP website following external peer review. Preliminary results:

- Glyphosate alters cell viability at concentrations >10mM, but only marginally as compared to positive controls.
- Formulations are more potent and efficacious than glyphosate at decreasing cell viability.
- Comparisons of dose response for reactive oxygen species vs. cell viability are ongoing.

NTP is also conducting a screening-level analysis of the existing literature using text mining and machine-learning approaches to better understand potential health outcomes related to glyphosate exposure.

Questions and comments

- Dr. Birnbaum inquired whether the screening-level analysis would look at formulations as well as pure glyphosate. Dr. DeVito indicated that it would.
- Dr. DeVito said the glyphosate concentration of the formulation would be lower than glyphosate itself due to the toxicity of the formulations. Formulations were diluted 1:300 at the highest in vitro concentrations, which often induced maximal loss in cell viability. He added that possession of confidential business information (CBI) had prevented testing individual constituents in a formulation. Dr. Birnbaum observed that no one is exposed to pure glyphosate.
- Dr. DeVito said the challenge in understanding the potential toxicity of glyphosate is that animal studies are all on pure glyphosate, while epidemiological studies are all on formulations, with co-exposure to the other constituents.
- Dr. DeVito said there has been interaction with Monsanto. The company has shared data on its oxidative stress and genotoxicity studies, and is awaiting the results of NTP's studies before further comment.
- In response to a question about whether Monsanto is required to submit data to EPA, Dr. Kavlock replied no, unless the data show a hazard.

B. Agency Activities

Regarding the presence of glyphosate in foods, Dr. Palmer Orlandi discussed commodity testing for glyphosate, noting that FDA has not conducted a great deal of that testing, but that a method for glyphosate detection has now been validated. Dr. Birnbaum commented that there have been many reports recently about glyphosate in the food supply. Dr. Orlandi noted that there hasn't been a lot of commodity testing because the processing of the commodities typically reduces levels to below threshold detection limits. FDA typically conducts screens for multiple pesticides.

ATSDR is working on a toxic profile for glyphosate, which is expected with six months for public comment. Dr. Birnbaum asked whether the profile would be for pure glyphosate or formulations. Dr. Birnbaum said she hoped it would address both.

VII. NTP Update

Dr. John Bucher briefed the committee on recent NTP developments. He related staff changes including recent hires and departures. He noted the peer reviews of three draft NTP Technical Reports (*p*-chloro-α,α,α-trifluorotoluene, 2,3-butanedione, and dietary zinc) and a draft Report on Carcinogens Monograph on Haloacetic Acids Found as Disinfections Byproducts. Dr. Bucher identified some upcoming activities including workshops and peer reviews and showed several examples of the redesigned NTP website.

Dr. Birnbaum announced that NIEHS had identified a top candidate for the NTP Associate Director position; however, with the NIH hiring freeze, the position is one of many in the agency in limbo.

Questions and comments

- Dr. Fitzgerald inquired about the status of NTP's reproductive/developmental toxicity studies of the caramel food color, 4-MEI (4-methylimidazole). Dr. Bucher said that although the studies are completed, data analysis has been delayed by IT problems.
- Dr. Fitzgerald asked about a recent report on lowered sperm levels. Dr. Birnbaum said that report (*Human Reproduction Update*, https://doi.org/10.1093/humupd/dmx022) contains little new information. It is the first systematic review to combine many studies and identify a possible trend.

VIII. Other Business

Dr. Birnbaum reiterated her call for committee members to consider nominations for study to NTP.

Dr. Howard noted that there is a nominee for Assistant Secretary for Health and Human Services, Dr. Brett Giroir, whose background is in research administration. The hearing is scheduled for August 1.

IX. Adjournment

Dr. Birnbaum adjourned the meeting at 3:50 pm.